National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Research Advances for Urologic Chronic Pelvic Pain Syndrome: Informing the Next Generation of Clinical Studies

Virtual Meeting
October 17–18, 2022

FINAL
EXECUTIVE SUMMARY

Background and Overview

Urologic Chronic Pelvic Pain Syndrome (UCPPS) encompasses both Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). UCPPS is defined by the hallmark symptom of chronic pain in such areas as the pelvis, urogenital floor, and external genitalia. Pain often is accompanied by diverse urologic symptoms, including urinary urgency and frequency. UCPPS is highly prevalent, and its impact on a patient's quality of life is enormous. Despite much past research, however, effective clinical management strategies are still lacking. There is a pressing need to translate new findings into improved, evidence-based clinical trials for UCPPS that ultimately will improve patient care.

The goal of the Research Advances for Urologic Chronic Pelvic Pain Syndrome: Informing the Next Generation of Clinical Studies meeting was to provide a forum for exchange of new insights into UCPPS and its underlying mechanisms and clinical characteristics. The meeting highlighted findings from NIDDK-supported Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and other investigators working in the UCPPS field, as well as advances in other areas that may inform the study of UCPPS. Collectively these efforts are providing a critical new evidence base to support future studies of UCPPS, including improved clinical trial designs.

The major scientific themes of the meeting sessions were—

- Phenotypic Subgrouping Strategies for Targeted Interventions
- Mechanistic Insights in Support of New Targets and Phenotypes
- Improved Evidence-Based Outcome Measures
- Designs for Potential Future UCPPS Clinical Trials Informed by New Research Insights

Breakout Groups for these themes met on both days and supported discussion of key considerations for potential future UCPPS clinical trials. In addition, several sessions—including virtual poster "flash talks," a session on measures and tools for improved UCPPS studies, and a special MAPP DataView tutorial Breakout Discussion—emphasized recent clinical advances and resources available for the UCPPS research community. More than 140 participants from across the United States and other countries registered and attended.

The meeting **Plenary Presentation** outlined the history and current state of the UCPPS field.

This was followed by an interactive **Patient Forum** to solicit and emphasize input from the patient perspective.

Patient Forum

Several patients were invited to share their experiences with UCPPS and describe how the disorder has affected their quality of life. The patients described such symptoms as recurring urinary tract infections; constant pelvic pain, urinary urgency, and frequency; overlapping issues, such as irritable bowel syndrome; and bladder spasms and shutdown. Each patient described the arduous diagnosis process and the negative effects of the disease on their daily lives, including difficulty with sleeping, inability to enjoy hobbies or travel, decreased enjoyment of sexual activities, and negative effects on mental health. The patients described their treatment regimens, which sometimes were painful and ineffective, and expressed their hopes for improved therapeutic options.

Measures, Tools, and Resources for Future UCPPS Studies Session

Participants highlighted key measures, tools, and resources that build on research in the UCPPS field including those from the NIDDK-sponsored Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU), Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN), and MAPP Research Network programs, as well as current opportunities for supporting future UCPPS clinical trials at the NIDDK:

- UCPPS symptom severity measures
  - Likert scales
  - Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index
  - Bladder Pain/Interstitial Cystitis Symptom Score
  - NIH Chronic Prostatitis Symptom Index
  - Genitourinary Pain Index (GUPI)
  - MAPP Pelvic Pain Severity (PPS) and Urinary Symptom Severity (USS) scales
  - LURN questionnaires (e.g., LURN SI-10, LURN SI-29, LURN Comprehensive Assessment of Self-Reported Urinary Symptoms)
  - Pain body maps
- General and treatment response measures
  - Brief Pain Inventory
  - Global Response Assessment (GRA)
- Methods for assessing chronic overlapping pain conditions (COPCs) for clinical research
  - International Classification of Diseases, Tenth Revision Computable Phenotype
  - COPCs Screener
- Covariate and stratification variables
  - Sex
  - Diagnosis
  - Widespread pain versus centralized pain
  - Genital pain versus bladder pain
  - Presence or absence of Hunner lesions (HLs)
  - Other psychosocial comorbidities
- MAPP resources and tools
  - MAPP Central Repository (e.g., clinical data, biospecimens, neuroimaging scans, protocols)
  - MAPP Data Codebook
  - MAPP DataView visualization toolkit
  - MAPP Research Network website
- CAIRIBU community resources

- NIDDK opportunities for support
  - Traditional investigator-initiated R01s proposing clinical trials (PA-20-183)
  - R01 applications proposing collaborative, interdisciplinary research in targeted areas (PAS-22-074)
  - Small, short-term pilot and feasibility clinical trials to obtain data to support larger, future trials (PAS-20-160)
  - High-risk trials, supported through a two-phase process
    - U34 Planning Phase (PAR-21-101)
    - U01 Cooperative Agreement Phase (PAR-21-102)
  - The NIDDK Central Repository and the MAPP Network DataView tool were also discussed as resources for the community

Scientific Session Moderated Discussions and Breakout Group Discussions

The meeting's Scientific Sessions and Breakout Groups focused on the four main topics listed above. Meeting speakers presented on themes related to each main topic. Following each Scientific Session Moderated Discussions were used to identify knowledge gaps and research opportunities relevant to these topics. The Breakout Groups further discussed these major themes to identify roadblocks to progress and opportunities for leveraging new insights to design improved, future clinical trials for UCPPS. A broad summary of key findings presented and selected, major discussion points for each main scientific theme is outlined below:

Phenotypic Subgrouping Strategies for Targeted Intervention

Emerging Studies

- Two emerging key IC/BPS subgroups are non-bladder centric (e.g., greater bladder capacity, no Hunner's Lesions (HLs), larger number of comorbid pain syndromes) and bladder centric (e.g., older age, more severe symptom scores, reduced bladder capacity, presence of HLs).
- MAPP-2 data suggests that identification of patients who are suspected of having HLs may inform selection of treatments, such as triamcinolone, fulguration, or cyclosporine A, in future trial designs.
- In women with IC/BPS and pelvic floor tenderness, studies show that pelvic myofascial physical therapy is more effective than global massage. Not all patients with pelvic floor tenderness, however, have a positive response to physical therapy.
- Studies have shown that patients with widespread pain are less likely to improve within 1 year and have distinct functional neural connectivity from other patient phenotypes.

Roadblocks/Gaps

- UCPPS is a heterogeneous syndrome with varied pathological mechanisms likely accounting for symptoms.
- Clinical trials composed of heterogeneous populations might have positive responses in a single group diluted by other cohorts, providing an overall negative result.
- Pelvic floor dysfunction is a common source of pain in UCPPS patients and when severe, may be associated with widespread pain. Symptoms related to pelvic floor dysfunction may be confused with other sources, i.e., bladder, vaginal, prostate.
- Little is known about pathophysiology related to the pelvic floor and its contribution to the symptoms of UCPPS.

- It is still not certain which strategy is best to identify the bladder-centric subgroup of UCPPS patients. Presence of HLs may be useful here.

Opportunities/Strategies

- The heterogeneous UCPPS population should be stratified into clinically meaningful phenotypes for individualized treatment trials.
- IC/BPS phenotypes—including HLs, widespread pain, pelvic floor tenderness, small bladder capacity, and psychosocial factors—can be used to characterize patients.
- Pelvic pain and urinary symptoms should be characterized separately. The PPS and USS indices show promise as practical and powerful tools for UCPPS assessment and phenotyping.
- Studies that focus on phenotypic subgroups should be balanced with studies that are inclusive of all chronic pelvic pain (CPP) patients.
- More studies that investigate targeted therapies are urgently needed.
- Lessons to be learned from other heterogeneous disorder groups include how to use biopsychosocial models, standardized clinical procedures, and dual-axis systems (i.e., physical diagnoses and psychosocial profiles), as well has how to improve data quality and generate machine-based diagnostic algorithms.
- Heterogeneous pain disorders often exist in conjunction with other pain and medical disorders that act in a loop to exacerbate one another. Cognitive behavioral therapy might be useful for treating such conditions.

Mechanistic Insights in Support of New Targets and Phenotypes

Emerging Studies

- MAPP neuroimaging studies have demonstrated that salience and medial sensorimotor systems in UCPPS patients display the most apparent dysfunction, providing a foundation for ongoing and future clinical trials of such treatment as repetitive transcranial magnetic stimulation.
- The role of activated microglia as mediators of pain and cognitive modulators is under investigation, with possible drug targets being identified.
- According to numerous studies, the Toll-like receptor 4 (TLR4) inflammatory response is strongly associated with pain driven by the central nervous system in IC/BPS and other COPCs.
- Molecular methods to study the urinary proteome and microbiome are being investigated for use in the diagnosis of UCPPS and the assessment of symptom severity.
- Pelvic examination scores correlate with worse urinary and pain symptoms, and patients with high scores may experience more centralized pain.
- The prospective observational Chronic Pain Risk Associated with Menstrual Pelvic Pain (or CRAMPP) study was designed to characterize uterine cross-organ influences on bladder pain and extend characterization of a group of women found to have both dysmenorrhea and silent bladder pain, who have biopsychosocial characteristics and pain sensitivity similar to women with BPS.

Roadblocks/Gaps

- Clinical trial design is a major challenge when disease mechanisms are unknown (i.e., matching treatment to mechanisms).
- The specific mechanisms underlying the segregation of patient pain responses and bladder symptoms, as well as widespread and centralized pain, are unclear.
- Trial results are often obscured by placebo effects.

Opportunities/Strategies

- Studies must be hypothesis-driven to counter the lack of mechanistic insight into UCPPS.
- Preclinical studies in animal models should be leveraged to generate, evaluate, and refine hypotheses.
- Differential responses to interventions by different subgroups can provide insights into UCPPS mechanisms of action.
- Future randomized controlled trials should include a broad spectrum of CPP patients and incorporate enough data to stratify patients by standardized phenotypes (e.g., body maps and pain sensation scores, urinary symptom scores, pelvic examination scores, neuroimaging categories).
- Adaptive trial designs should be incorporated to mitigate placebo effects.
- Multimodal pain sensitivity likely reflects higher order nervous system dysregulation and may help provide insight into the mechanisms and progression of pelvic disease.
- The nervous and immune systems, which likely interact to modulate pain sensation, are both potential therapeutic targets.
- UCPPS therapy modalities (e.g., pelvic floor therapy) should be standardized.

Improved Evidence-Based Outcome Measures

Emerging Studies

- A MAPP Research Network prospective cohort study was conducted to quantify thresholds of symptom-based, patient-reported outcomes at which UCPPS patients feel better and to determine whether thresholds for these clinically important differences vary by patient factors. The study resulted in empirically determined trial endpoints for UCPPS and showed that certain patient subgroups require greater absolute changes in UCPPS to feel improvement.
- A longitudinal "diary" study of symptom flare triggers showed a wider range of flare duration and a more frequent flare frequency than expected, prompting larger flare survey studies in which flare duration, frequency, symptom intensity, health care utilization, and level of bother were assessed. Long-term effects of flares included changes in habit to avoid flares (e.g., diet changes), reduced social interaction, avoidance of sexual relationships and relationship strain or failure, career challenges, and severe mental health effects.

Roadblocks/Gaps

- Less-than-obvious quality-of-life outcomes (e.g., mental health, sleep, disruption of daily activities) are a priority for UCPPS patients, but they have been overlooked historically and are challenging to measure in a standardized manner.
- Assessment tools have not been optimized for maximum benefit to the patient, and clinical data have not been linked to actions in the clinic.
- Patient-reported outcomes can involve inaccurate reporting associated with recall bias, especially in older patients.
- Several outcome measures used in the past are not recognized or approved by the U.S. Food and Drug Administration (FDA).
- Some broader questions related to overlap between UCPPS pain and COPCs still remain to be addressed.

Opportunities/Strategies

- The GRA is recommended as a primary study endpoint, although separate assessments are also needed for pain and urinary symptoms.

- Secondary endpoints should include PPS and USS subscales, which require GUPI and ICSI assessments.
- Standardized assessments for widespread pain and pelvic muscle tenderness have been beneficial and should continue to be incorporated into clinical trials.
- Biological, psychological, and social factors should be separated during data analysis.
- UCPPS patients might benefit from strategies that reduce flare frequency, even if these strategies do not reduce typical pain levels, and flare characteristics should be considered as additional outcomes in future studies.
- The ability to measure disruption of daily activities in a standardized manner would be beneficial when measuring treatment effectiveness.
- Data related to mental health and sleep should be collected, and modifiable antecedents of these symptoms should be identified.
- Symptom monitoring with patient alerts can improve quality-of-life outcomes.
- Bioinformatic data collection and data-driven decision-making should be integrated into the clinic workflow.
- Questionnaires potentially could include information that overlaps with and informs other research networks investigating chronic pain.

Designs for Potential Future UCPPS Clinical Trials Informed by New Research Insights

Emerging Studies

- The Understanding Pathophysiology and Determining Appropriate Treatments (or UPDATe) study is underway to determine whether vestibulodynia patients might benefit most from peripheral treatment and whether patients with vestibulodynia and a COPC might benefit most from centrally targeted treatment.
- The primary objective of the recent Biomarkers for Evaluating Spine Treatments (or BEST) study was to optimize treatment effectiveness by generating an algorithm to assign sequences of up to two interventions based on each patient's phenotypic markers and their response to the initial treatment. Such trials can be adapted for the study of UCPPS treatments.
- Programs like Nephrotic Syndrome Study Network (or NEPTUNE) Match, which uses molecular and clinical phenotyping to match patients with clinical trials targeting specific biological pathways, can serve as models for clinical trials involving precision interventions.

Roadblocks/Gaps

- Past UCPPS clinical trials have failed to stratify heterogenous patient populations and did not include targeted interventions.
- Clinical trials likely have been hampered by too many inclusion and exclusion criteria.
- Standardized methods for dealing with multiple phenotypes have not yet been implemented in past UCPPS studies.
- Despite its promise, several challenges are associated with adaptive trial methodology, including how many randomizations and treatment combinations can realistically be studied; the length of treatment period sufficient to observe a treatment response; the length of "wash-out" period needed between treatments; and the number of patients and sites needed to observe significant results.
- Barriers to patient recruitment include concerns about data privacy, dependent care, inadequate reimbursement, negative experiences with research studies or medications, time commitment, and transportation.

Opportunities/Strategies

- The implementation of adaptive platform trial designs will enable tailoring of treatment to unique patient symptoms and convergence on effective treatments, reducing the risk of failed or inconclusive studies.
- Characteristics of Sequential Multiple Assignment Randomize Trial (or SMART) adaptive trial design include the following:
    - All individuals participating in all stages of the trial
    - Randomization of patients before providing treatment
    - Categorizing responders and non-responders after a defined treatment period
    - Providing non-responders with a new treatment after additional rounds of randomization
- Several promising interventions can be assessed in new and improved trials:
    - Amitriptyline/nortriptyline or pregabalin for widespread pain patterns
    - Pelvic floor therapy for pelvic floor tenderness
    - PPS and hydroxyzine for bladder-centric symptoms
    - Cognitive behavioral therapy for psychosocial symptoms
- Patients should be stratified at baseline.
- TLR4 levels should be measured at baseline and then serially throughout treatment to serve as a possible predictor of treatment response.
- Patient recruitment strategies might include clinician champions, engagement with patient families, interactive websites, and systematic methods for contact and scheduling. Engagement and retention strategies should focus on return of value for patients and all other stakeholders to ensure diverse datasets with limited biases.

Final Discussion of Major Emerging Themes: Evidence-Based Trials for UCPPS

In a final discussion session, meeting participants provided feedback on the emergent themes. The following points were noted:

- The field is working to transition from prior trial designs to more evidence-based/precision medicine trials. The MAPP Network has enhanced our evidence base to design new trials.
- Important to determine "What success looks like" for future trials.
- Clinical trial design and efficiency should be improved. Phenotyping schemes, subgroup assignments, treatment pathways, and biomarkers of treatment action should be optimized for each patient and to maximize the useful data obtained from each trial. New trial designs to optimize efficiency should be considered.
- Classification schemes of identified subgroups vary widely (e.g., symptomatic classification, anatomic classification). More than one phenotypic dimension might be necessary for categorizing patients and identifying potential targeted interventions. Important to match a modifiable pathway (mechanism) to a phenotype in trials.
- Data collection should be maximized to include information about COPCs, infections, flare burdens, sleep quality, and other psychosocial factors.
- Key design points to consider: Clinical trial question (start) – Population – Intervention – Outcomes – Control group – Length.
- Clinical trial outcomes should be approved by the FDA and measure clinically significant differences.
- Symptom flares diminish patient quality of life in a manner that exceeds effects measured using average scores. Additional information about symptom flares is needed, including how they affect enrollment and outcome assessment in clinical trials.
- Patient participation, which can be incorporated via patient advisory boards and one-on-one interviews, should be a factor when designing clinical trials. For example: Ask prospective participants, "Is this an important question to address?"

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